Caffeine for apnea of prematurity: a neonatal success story

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Abstract: Caffeine, a methylxanthine and nonspecific inhibitor of adenosine receptors, is an example of a drug that has been in use for more than 40 years. It is one of the most commonly prescribed drugs in neonatal medicine. However, until 2006, it had only a few relatively small and short-term studies supporting its use. It is thanks to the efforts of Barbara Schmidt and the Caffeine for Apnea of Prematurity (CAP) Trial Group that we now have high-quality and reliable data not only on short-term but also long-term outcomes of caffeine use for apnea of prematurity. CAP was an international, multicenter, placebo-controlled randomized trial designed to determine whether survival without neurodevelopmental disability at a corrected age of 18 months is improved if apnea of prematurity is managed without methylxanthines in infants at a high risk of apneic attacks. CAP was kept simple and pragmatic in order to allow for maximum generalizability and applicability. Infants with birth weights of 500-1,250 g were enrolled during the first 10 days of life if their clinicians considered them to be candidates for methylxanthine therapy. The most frequent indication for therapy reported in CAP was treatment of documented apnea, followed by the facilitation of the removal of an endotracheal tube. Only about 20% of the neonatologists in the trial started caffeine for the prevention of apnea and the findings of CAP cannot automatically be extrapolated to an exclusive prophylactic indication. However, recent data suggest that the administration of prophylactic methylxanthine by neonatologists is now common practice.

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Caffeine for Apnea of Prematurity: A Neonatal Success Story

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Caffeine · Apnea of prematurity · Prophylactic methylxanthine therapy

Abstract
Caffeine, a methylxanthine and nonspecific inhibitor of adenosine receptors, is an example of a drug that has been in use for more than 40 years. It is one of the most commonly prescribed drugs in neonatal medicine. However, until 2006, it had only a few relatively small and short-term studies supporting its use. It is thanks to the efforts of Barbara Schmidt and the Caffeine for Apnea of Prematurity (CAP) Trial Group that we now have high-quality and reliable data not only on short-term but also long-term outcomes of caffeine use for apnea of prematurity. CAP was an international, multicenter, placebo-controlled randomized trial designed to determine whether survival without neurodevelopmental disability at a corrected age of 18 months is improved if apnea of prematurity is managed without methylxanthines in infants at a high risk of apneic attacks. CAP was kept simple and pragmatic in order to allow for maximum generalizability and applicability. Infants with birth weights of 500–1,250 g were enrolled during the first 10 days of life if their clinicians considered them to be candidates for methylxanthine therapy. The most frequent indication for therapy reported in CAP was treatment of documented apnea, followed by the facilitation of the removal of an endotracheal tube. Only about 20% of the neonatologists in the trial started caffeine for the prevention of apnea and the findings of CAP cannot automatically be extrapolated to an exclusive prophylactic indication. However, recent data suggest that the administration of prophylactic methylxanthine by neonatologists is now common practice.

Pharmacological Studies in Children

Despite the introduction of new legislation in the European Union in 2007 aimed at increasing the amount of pediatric data on medicinal products, off-label drug use in pedriatric patients in hospitals is still common [1]. According to a nationwide population-based investigation of pediatric drug use at Swedish hospitals, the percentage of unlicensed and off-label drug use, i.e. 7.4 and 57%, respectively, is highest in neonates [1]; similar reports have also emerged in other countries [2, 3]. Neonates and especially preterm infants are particularly vulnerable because of their small body size and immature body organs

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[4]. Neonatal clinical drug trials of a high standard and with sufficient sample sizes to allow firm conclusions are needed, not only for the investigation of new and future drugs but also for older products that are widely used in clinical practice without sufficient data on efficacy and safety, e.g. inhaled steroids for the prevention and/or treatment of bronchopulmonary dysplasia [5]. This is, however, going to take a long time, due to the substantial number of such products currently still on the market [1]. The extensive use of off-label and unlicensed drugs as well as old and widely used medicines will probably remain as no real legal pressure has been exerted in this domain and the financial incentive for pharmaceutical companies to perform clinical studies in children is limited. Thus, the role of public funding agencies and academic investigators is crucial in this field.

One example of a drug that has been used for more than 40 years and was, until 2006, one of the most commonly prescribed drugs in neonatal medicine with only a few relatively small and short-term studies supporting its use, is caffeine, a methylxanthine and a nonspecific inhibitor of adenosine receptors [6]. It is thanks to the efforts of Barbara Schmidt and the Caffeine for Apnea of Prematurity (CAP) Trial Group, together with the Canadian Institutes of Health Research (CIHR) and the National Health and Medical Research Council of Australia (NHMRC) who funded the trial, that we now have high-quality and reliable data not only on short-term but also long-term outcomes of caffeine use for apnea of prematurity [7, 8]. In 1999, when CAP started patient recruitment, there was reasonable doubt about the safety of caffeine in very preterm infants and genuine uncertainty in the expert neonatal community whether it would be beneficial in the long term, a situation which describes the principle of clinical equipoise [6]. Fifteen years later, the neonatal community can be reasonably sure that the benefits of caffeine treatment for apnea of prematurity outweigh the risks, and the story of caffeine in neonatology can indeed be considered a success.

The Discovery of Caffeine

Coffee beans have been chewed in the highlands of Ethiopia for hundreds of years [9]. One story of the origin of coffee as a beverage is the myth of Kaldi the Ethiopian goatherd [9]. The story goes that Kaldi noticed the stimulating effects of coffee beans when his goats chewed the red cherries of a certain bush, which made him try the berries himself. Their energizing effect prompted him to bring the berries to a holy man in a nearby monastery. However, the saint disapproved of their use and threw them into the fire. Just afterwards, an enticing aroma emerged from the flames. The roasted beans were quickly taken out of the fire, pulverized and added to hot water, leading to the world's first cup of coffee [9]. While the story of Kaldi is a myth, it is in fact likely that Ethiopians were the first to have recognized the stimulating effect of the coffee plant, a member of the Rubiaceae family [9]. According to this theory, which takes its support from traditional tales and current practice, tribesmen collected the ripe coffee berries from wild bushes, crushed them with stone mortars and mixed them with animal fat, forming small balls that they carried with them in military conflicts [9].

Nevertheless, the most popular formulation of caffeine has been, and still is, as a beverage, including tea and coffee. Tea has been consumed for thousands of years in Asia. The Taoists and Zen Buddhists relied on the caffeine in tea for their meditations. The notion that tea is an indispensable ingredient of the elixir of life has been ascribed to Lao-tzu, the founder of Taoism, in a Chinese text of the 1st century BC [9]. Later, his followers, the Taoist alchemists, called it the 'froth of the liquid jade' [9]. Bodhidharma, who founded the school of Buddhism based on meditation which later became Zen Buddhism is said to have been involved in the introduction of tea to China [9]. One T'ang dynasty story tells that Bodhidharma cut off his own eyelids in anger for having fallen asleep after nine continuous years of meditation. The eyelids fell to the ground and took root, transforming into tea bushes that would sustain meditations forever after [9].

In the 15th century, Sufis may have been the first to use caffeine expressly for its pharmacological effects. Sufism requires of its followers that they perform a remembrance ritual to the glory of God. Before performing this ritual, coffee was shared by the Sufis in a ceremony described by Jaziri Avion [9, 10]:

They drank it every Monday and Friday eve, putting it in a large vessel made of red clay. Their leader ladled it out with a small dipper and gave it to them to drink, passing it to the right, while they recited one of their usual formulas, 'There is no God, but God, the Master, the Clear Reality'.

From the example of the Sufi conclaves, the coffeehouse was born. By 1510, coffee had spread from the monasteries of the Yemen into general use in Islamic capitals such as Cairo and Mecca [9]. At one point, Mecca's police-chief banned the consumption of coffee, but soon after, the Sultan of Cairo, a coffee-drinker himself,

reversed the ban [9]. In 1555, coffee and the coffeehouse were brought to Constantinople by Hakam and Shams, Syrian businessmen from Aleppo and Damascus, respectively, and to this day, coffee and coffeehouses are very popular in Turkey and its neighboring countries [9, 10].

An encounter between a scientist and a poet resulted in isolated caffeine first being revealed to the world. The discovery was made by a young physician, Friedlieb Ferdinand Runge, in 1819, after an encounter with the 70-year-old Johann Wolfgang von Goethe, one of the world's greatest poets [9, 11]. Runge was studying under the chemist Döbereiner, who brought one of Runge's main discoveries to Goethe's attention: the potential of Belladonna extract to dilate the pupil [9]. Goethe, who was not only a poet but also an amateur scientist, invited Runge to visit him to demonstrate this phenomenon. Runge accepted the invitation and performed the experiment by placing a few drops of Belladonna extract into the eye of a cat that Runge had brought with him [9]. Goethe was intrigued and presented Runge with a box of rare Arabian mocha coffee beans, inviting him to perform an analysis of the contents. This led to the isolation of the world's first sample of pure caffeine [9].

How Does Caffeine Work?

Caffeine is a methylxanthine and acts as a nonspecific inhibitor of 2 of the 4 known adenosine receptors [12]. The receptors that transduce adenosine action are the A1, A2a, A2b and A3 adenosine receptors [6]. Adenosine is a purine nucleoside that is produced naturally in human tissues, including the brain [11]. Few signaling molecules have the potential to influence the developing human organism like the nucleoside adenosine [13]. Adenosine levels increase rapidly with inflammation [13]. Two known scenarios that cause an imbalance between adenosine synthesis and adenosine breakdown are hypoxia and ischemia [12]. The extracellular concentration of adenosine rises in the brain when energy demand outstrips energy supply and brain cells are at risk of dying [11]. In the postnatal period, A1 adenosine receptor activation may contribute to the injury of white matter in the preterm infant by altering oligodendrocyte development [13]. Adenosine slows things down in order to preserve precious energy [11]. In models of perinatal brain injury, caffeine is neuroprotective against periventricular white matter injury and hypoxic-ischemic encephalopathy [13].

Caffeine as a Treatment for Apnea of Prematurity

The CAP trial was launched to resolve the uncertainty about the long-term effects of caffeine used as a respiratory stimulant in preterm infants [11]. This international, multicenter, placebo-controlled randomized trial was designed to determine whether survival without neurodevelopmental disability at a corrected age of 18 months is improved if apnea of prematurity is managed without methylxanthines in infants at a high risk of apneic attacks [7]. CAP was one of the largest neonatal trials conducted and was deliberately kept simple and pragmatic in order to allow for maximum generalizability and applicability under real-world conditions. Infants with a birth weight of 500–1,250 g were enrolled during the first 10 days of life if their clinicians considered them to be candidates for methylxanthine therapy [7]; 2,006 infants were randomly assigned to receive either caffeine or placebo. Following the recommendation of the external safety monitoring committee, the protocol specified secondary short-term outcomes were published before the complete ascertainment and publication of the primary outcome [7]. The major findings for the secondary short-term outcomes included a reduced incidence of bronchopulmonary dysplasia (36% with caffeine and 47% with placebo; OR 0.63 and 95% CI 0.52–0.76; $p < 0.001$). Caffeine also reduced weight gain for the first 3 weeks after the start of therapy. Head circumference was not affected and the rates of death, ultrasonographic signs of brain injury and necrotizing enterocolitis were similar in the caffeine and placebo groups [7].

In 2007, the primary outcome data of CAP were published [8]. The primary outcome was a composite of death, cerebral palsy, cognitive delay (defined as a Mental Developmental Index score of <85 on the Bayley Scales of Infant Development II), hearing loss requiring amplification or bilateral blindness at a corrected age of 18–21 months [8]. Of the infants for whom adequate data on the primary outcome were available, 377 of 937 (40.2%) assigned to caffeine died or survived with a neurodevelopmental disability and 431 of 932 (46.2%) assigned to placebo died or survived with neurodevelopmental disability (OR 0.77, 95% CI 0.64–0.93; $p = 0.008$) [8].

When 1,640 (84.9%) of the 1,932 study children who were eligible were assessed at the age of 5 years to determine whether neonatal caffeine therapy has lasting benefits or newly apparent risks at early school age, the difference between the caffeine and placebo groups was no longer statistically significant [14]. The outcome assessed at this 5-year follow-up was a combined one of death or

survival to 5 years with 1 or more of the following: motor impairment (defined as a Gross Motor Function Classification System level of 3–5), cognitive impairment (defined as a Full-Scale IQ <70 on the Wechsler Preschool and Primary Scale of Intelligence III), behavioral problems, poor general health, severe hearing loss and bilateral blindness [14].

Economic Aspects of Caffeine for Apnea of Prematurity

Caffeine not only reduces the rate of bronchopulmonary dysplasia and improves the rate of survival without neurodevelopmental disability at 18–21 months in infants with a birth weight of 500–1,250 g, it is also a cost-saving therapy compared with placebo [15]. In a retrospective economic evaluation alongside the CAP study using individual-patient data, Dukhovny et al. [15] found that the probability of caffeine being not only effective but also cost-saving was >99%. This effect was, in large part, attributed to the reduced number of days on positive pressure ventilation. In their analysis, the authors included the direct medical costs for the insurance payer or the hospital, but excluded the costs for parents and society. Their cost assumptions were based on Canadian prices to resource tallies from all trial participants and, from today's perspective, included a relatively low cost of caffeine citrate (CAD 0.21/mg). Since then, prices for caffeine have risen substantially as it is now a licensed product for the treatment of apnea of prematurity in some countries. However, the results of the economic evaluation were robust to a substantial increase in the individual resource items, including the price of caffeine citrate. Increasing the price of caffeine citrate 100-fold from CAD 0.1, caffeine still remained not only effective but also cost-saving [15].

Caffeine as Prophylaxis for Apnea of Prematurity

The eligibility criteria of the CAP study were deliberately broad and pragmatic. Infants could be randomized in the first 10 days of life when caregivers considered them to be candidates for methylxanthine therapy [7]. The most frequent indication reported in the CAP study was the treatment of documented apnea (41.5%), followed by the facilitation of removal of an endotracheal tube (36%). Only 22.5% of the neonatologists in the trial started caffeine for the prevention of apnea [7]. Thus, the findings of the CAP study cannot automatically be extrapolated to a prophylactic indication, even if it is reassuring that in a post hoc subgroup analysis performed for the indication for starting on the study drug, little evidence of heterogeneity of treatment effect for any outcome assessed was found [16]. Post hoc subgroup analyses also suggest evidence of variable beneficial effects of caffeine. Infants receiving respiratory support appeared to derive more neurodevelopmental benefits from caffeine than infants not receiving support [16]. In addition, earlier initiation of caffeine (<3 days) may be associated with a greater reduction in time on ventilation than later initiation (>3 days) [16]. However, it is important to stress that although effect sizes and directions of effect of caffeine varied in the subgroups, there was no evidence of harm that reached statistical significance [16]. When applying the CAP study findings to individual patients, one should keep the subgroup analyses results in mind. From a methodological point of view, however, caution should be exercised in the interpretation of these subgroups. There was no stratification for clinical indication, and the time of starting on the study drug and level of respiratory support were not recorded in the CAP study. Furthermore, the sample size was not calculated based on these subgroups [16].

As pointed out above, the findings of the CAP study cannot automatically be extrapolated to an exclusively prophylactic indication or to all preterm infants, regardless of their gestational age and risk for apnea of prematurity. However, in a recent cross-sectional survey of neonatologists in Thailand, Lebanon, Australia and a representative sample in the USA with regard to the management of apnea of prematurity with a response rate of 50%, the use of prophylactic methylxanthine was very common (62%) among neonatologists at all 4 locations [17].

Tribute to Barbara Schmidt

Certain names come to mind when considering the people who made the investigation of caffeine therapy for apnea of prematurity a success story. Kuzemko and Paala [18] published the first report of methylxanthine use for apnea of prematurity in 1973. Aranda et al. [19] reported the first use of caffeine therapy for apnea in the English biomedical literature. When it comes to controlled clinical trials, one name clearly stands out: Barbara Schmidt. An encounter between two people with different professional backgrounds, Runge the scientist and Goethe the poet, resulted in isolated caffeine first being revealed to

the world, but a clinical trial designed chiefly by one person, Barbara Schmidt, combining her expertise in clinical epidemiology and neonatology, is what demonstrated clearly the important benefits of caffeine therapy for apnea of prematurity. Currently a Professor of Pediatrics and a Senior Scholar in the Center for Clinical Epidemiology and Biostatistics at the School of Medicine, University of Pennsylvania, she is also a staff neonatologist in the Division of Neonatology at the Children's Hospital of Philadelphia and the University of Pennsylvania Health System. Barbara Schmidt's research focuses on collaborative neonatal randomized trials that have clinically important, long-term outcomes, not only for caffeine but also for other drugs such as indomethacin [20]. When neonatologists are asked what the main research findings during the past years are that have changed their approach to clinical practice, many cite Barbara Schmidt's caffeine (CAP) study. This study has contributed substantially to the fact that caffeine for the treatment of apnea of prematurity can be considered a great neonatal success story [21].

Disclosure Statement

The authors have nothing to disclose.

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